REMARKS

Claims 1 – 10, 43 – 45 and 49 are pending in the application. No claims have been amended or added. Accordingly, claims 1 – 10, 43 – 45 and 49 will remain pending in the application

35 U.S.C. §112, first paragraph

Enablement

Claims 1-3, 43-45 and 49 are rejected under 35 U.S.C. §112, first paragraph as allegedly lacking enablement (Office Action, p. 3). Claims 1-3, 43-45 and 49 are directed to a glycoconjugate comprising a bioactive agent and a targeting compound (i.e., a glycoprotein, glycolipid or carbohydrate) joined by a modified UDP galactose acetyl group (UDP-GalNAc), and wherein the modified UDP-GalNAc comprises a ketone group attached to the C2 position of the galactose ring.

The Examiner argues that "the specification, while being enabling only for a targeted glycoconjugate comprising a specific bioactive agent as shown the specific anticancer agent listed at pages 14 – 15 and a specific targeting compound such as the ones listed at page 19 wherein the bioactive agent and the targeting compound are joined by a modified UDP-galactose-Acetyl group (UDP-GalNAc) having a ketone functional group appended at the C-2 position of the galactose ring using the mutant Y289L galactose transferase for detection assays, **does not** reasonably provide enablement for (1) any targeted glycoconjugate comprising any and all bioactive agent and any and all targeting compound wherein the bioactive agent and the targeting compound are joined by a modified UDP galactose acetyl group (UDP-GalNAc) compris(ing) a ketone group attached to the C2 position of the galactose ring" as claimed. Applicants respectfully disagree and traverse the rejection.

The Office bears the initial burden of establishing a reasonable basis to question the enablement of the claimed invention. *In re Wright*, 999 F.2d 1557, 1562 (Fed. Cir. 1993). Where Applicants describe methods of making and using the invention, Applicants' specification **must** be accepted as providing an enabling disclosure unless the Examiner has evidence showing that **the truthfulness of such statements is in doubt**. M.P.E.P. 2164.04. "Burden on the Examiner under the Enablement Requirement." Specifically, the M.P.E.P. states:

> A specification disclosure which contains a teaching of the manner and process of making and using an invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented **must be taken as being in compliance with the enablement requirement of** 35 U.S.C. 112, **first paragraph, unless there is a reason to doubt the objective truth of the statements contained therein** which must be relied on for enabling support. (emphasis added)

Not only must the truth of Applicant's statements be in doubt, but the Examiner must provide evidence to show why the Examiner doubts the veracity of Applicants' specification.

> **[I]t is incumbent upon the Patent Office, whenever a rejection on this basis is made, to explain why it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence** or reasoning which is inconsistent with the contested statement. Otherwise, there would be no need to go to the trouble and expense of supporting his presumptively accurate disclosure. *In re Marzocchi* 439 F.2d 220, 224 (emphasis added)

Applicants respectfully submit that the Examiner has not submitted any evidence to doubt the truth or accuracy of any statement in Applicants' disclosure which is relied on for enabling support. In the absence of this showing, the rejection alleging lack of enablement is improper and must be withdrawn.

Nevertheless, the Examiner argues that "[e]nablement is not commensurate in scope with *how to use* any unspecified targeted glycoconjugate comprising any bioactive agent and any unspecified targeting compound for the claimed targeted glycoconjugate as a pharmaceutical composition or for use in any." (Office Action, p.4; Examiner's emphasis). In support of the enablement rejection, the Examiner argues that "[t]he specification discloses only labeling of CREB or bovine lens α-crystallin using recombinant O-Glc-NAc glycosylated CREB and the mutant Y289L O-GlcNAc glycosyltransferase... The specification discloses only modified UDP galactose-Acetyl group (UDP-GalNAc) having a ketone functional group appended at the C-2 position of the galactose ring using mutant Y289L galactose transferase." Other than the specific name bioactive agent and antibody attached to the C2 position of the galactose ring using modified enzyme Y289L O-GlcNAc glycosyltransferase, the specification does not teach the structure associated with function of any active agent. comprising the specific bioactive agent mentioned above and the specific targeting compound mentioned above...the specification does

not teach the use of targeted glycoconjugate comprising any bioactive agent linked to any targeting compound via modified UDP galactose acetyl group attached to the C2 position of the galactose ring for treating any disease, much less for preventing all diseases." (Office Action, p. 4 – 5). Applicants respectfully disagree.

Applicants respectfully invite the Examiner's attention to M.P.E.P. §2164.01(c) which provides guidance on how to determine whether the "how to use" element of enablement has been satisfied:

> **In contrast, when a compound or composition claim is not limited by a recited use, any enabled use that would reasonably correlate with the entire scope of that claim is sufficient to preclude a rejection for nonenablement based on how to use.** If multiple uses for claimed compounds or compositions are disclosed in the application, then an enablement rejection must include an explanation, sufficiently supported by the evidence, why the specification fails to enable each disclosed use. **In other words, if any use is enabled when multiple uses are disclosed, the application is enabling for the claimed invention**. (emphasis added).

The invention as claimed is a targeted glycoconjugate comprising a bioactive agent and a targeting compound, wherein the targeting compound is a glycoprotein, glycolipid or carbohydrate, and wherein the bioactive agent and targeting compound are joined by a modified UDP galactose acetyl group (UDP-GalNAc), and wherein the modified UDP-GalNAc comprises a ketone group attached to the C2 position of the galactose ring. Claims 1, 2, and 49 are directed to a glycoconjugate (i.e., a compound), which is not limited to a recited use. Furthermore, Applicants have exemplified that CREB or bovine lens α-crystallin can be labeled using recombinant O-Glc-NAc glycosylated CREB and the mutant Y289L O-GlcNAc glycosyltransferase and the generation. This level of enablement is at least acknowledged by the Examiner at pages 4-5 of the Office Action. Therefore, Applicants respectfully submit that the claims are enabled according to the standard set forth in M.P.E.P. §2164.01(c), which states that any enabled use is enabling for multiple uses, and respectfully request withdrawal of the rejection.

In support of the enablement rejection, the Examiner goes to great lengths to point out information that is allegedly missing from Applicants' disclosure regarding binding specificity, structure, and *in vivo* data regarding the compounds of the invention (Office Action at pages 5-8) but makes absolutely no showing as to why one skilled in the art could not supply the missing

information without undue experimentation. Without more, the Examiner must accept the truth of Applicants' assertions.

The standard set forth for enablement in 35 U.S.C. §112, first paragraph, requires that Applicants provide a description of the invention sufficient "to enable any person skilled in the art to which it pertains..,to make and use" the invention. The standard for determining enablement is whether one of ordinary skill would need to engage in undue experimentation to practice the claimed invention. (*In re Wands*, citations omitted; MPEP §2164.01). "The test is not merely quantitative, since a considerable amount of experimentation is permissible, if is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed." MPEP §2164.06, citing *In re Wands*. (Citations omitted.) Moreover, Applicant does not need to demonstrate therapeutic effects for particular diseases to enable the invention as claimed. According to the MPEP §2164.02, "compliance with the enablement requirement of 35 U.S.C. 112, first paragraph, does not turn on whether an example is disclosed."

In view of the disclosure and guidance provided by the application, the state of the art at the time the application was filed and the high level of skill in the art at the time the application was filed, Applicants submit that one skilled in the art would be able to practice the claimed invention using no more than routine experimentation.

That is, experiments using binding assays routine in the art can be used to test the binding specificity of any of the targeting compounds that have been labeled according to the methods of the invention, or clinical studies set up according to methods routine in the art can be used to obtain clinical data on a targeting compound labeled according to the methods of the invention. The test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue. *In re Angstadt*, 537 F.2d 498, 504, 190 USPQ 214, 219 (CCPA 1976). Given the knowledge available (e.g., regarding the targeting compounds, clinical trials, etc.) at the time of the invention, it is especially true that undue experimentation is not required to determine these properties of the glycoconjugates of the invention.

Regarding the structure of the glycoconjugates of the invention, Applicants have demonstrated in the Examples the ability of GalT to label the peptide TAPTS(O-GlcNAc)TIAPG, which encompasses an O-GlcNAc modification site within the protein CREB. Applicants used wild-type GalT and showed that only partial transfer of the keto-sugar was

observed by LC-MS, however when the Y289L mutant was used there was greater activity and complete conversion. (see page 40, line 14 – 22). Further, Applicants show that the same strategy can be used for the labeling of the O-GlcNAc glycosylated protein CREB (see, e.g. page 45, line 8 – 23). The specification at page 10, line 15 states, "the targeting compound (T)…is covalently bonded to a saccharide residue (S) with the use of a galactosyltranserfase enzyme, preferably beta-1,4-galactosyltransferase (GalT). In one embodiment of the invention, a modified saccharide (S) is covalently associated with the targeting compound with the use of a genetically engineered GalT, such as Y289L GalT (as discussed above). The targeting compound can be any naturally occurring glycoprotein, glycolipid or carbohydrate or can be engineered, through chemical or recombinant techniques. For example, if the targeting compound does not include a GlcNAc residue, the compound can be engineered, either through recombinant or chemical techniques known in the art, so as to include such a residue. Preferably, the targeting compound includes an N-acetylglucosamine (GlcNAc) residue."

The specification teaches at page 11 beginning at line 5, various methods that can be used to bind a bioactive agent to the modified saccharide, depending on the structure of the bioactive agent. The specification teaches that the C2 position is favorable over other positions on the galactose ring because GalT has been shown to tolerate unnatural substrates containing minor substitutions at the C2 positions. Applicants teach appending the ketone functionality particularly at the C-2 position of the galactose ring. At page 48 of the specification, Applicants describe a strategy for the rapid and sensitive detection of O-GlcNAc glycosylated proteins, where experiments show that "the ketone functionality was appended at the C-2 position of the galactose ring because GalT has been shown to tolerate unnatural substrates containing minor substitutions at the C-2 positions, including 2-deoxy, 2-amino, and 2-N-acetyl substituents (Ian et al., 2001; Wong et al., 1995) (and)… 2-deoxy-Gal was transferred at rates comparable to Gal, whereas 3-, 4, and 6-deoxy-Gal were transferred at reduced rates." (p. 48, emphasis added).

Applicants have further exemplified that antibodies can be galactosylated with Y289L GalT having a chemical handle at the C2 position in Bioconjugate Chem. 2009, 20, 1228 – 1236 (provided in the response dated September 8, 2009). Applicants describe the utility of Y289L GalT to transfer a sugar residue with C2-keto-Gal (or GalNAz) from their UDP derivatives to the N-acetylglucosamine residue of glycoproteins or glycopeptides. (see, e.g. Figure 5 on page 1233). Moreover, Applicants teach that the conjugation technology is a viable method that can

be used for detection and targeting therapies. (see, p.1229). In Bioconjugate Chem. 1009, 20, 1383- 1389 (provided in the Response dated September 9, 2009), Applicants describe the biological activity of the described glycoconjugates. For example, Applicants describe C-terminal extended fusion polypeptides of recombinant scFv fusion proteins that are used as the acceptor substrate for human polypeptide-alpha-N-acetylgalactosaminyltransferase II that transfers either GalNAc or 2-keto-Gal from their respective UDP-sugars to the side-chain hydroxyl group of the Thr residue(s). The fusion scFv proteins with the modified galactose are then conjugated with a fluorescence probe, Alexa488, that carries an orthogonal reactive group. The fluorescence labeled scFv proteins bind specifically to a human breast cancer cell line (SK-BR-3) that overexpresses the HER2 receptor, indicating that the in vitro folded scFv fusion proteins are biologically active and the presence of conjugated multiple Alexa488 probes in their C-terminal end does not interfere with their binding to the antigen.

It is respectfully submitted that these disclosures sufficiently enable the glycoconjugates of the invention with regard to their structural properties. That is, no undue experimentation regarding structure is required to obtain the glycoconjugates of the invention, and one skilled in the art would be able to practice the claimed invention using no more than routine experimentation.

Taken together, the teachings of the specification and knowledge of one of skill in the art enables one of skill in the art to practice the full scope of the claimed invention without having to resort to undue experimentation. Applicants accordingly request that the rejection be reconsidered and withdrawn.

Written Description

Claims 1 – 3, 43 – 45 and 49 were rejected under 35 U.S.C. §112, first paragraph, for allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention. (Office Action, p.10 - 11). Applicants respectfully disagree.

The present claims are directed to a targeted glycoconjugate comprising a bioactive agent and a targeting compound, wherein the targeting compound is a glycoprotein, glycolipid or carbohydrate, and wherein the bioactive agent and targeting compound are joined by a modified

UDP galactose acetyl group (UDP-GalNAc), and wherein the modified UDP-GalNAc comprises a ketone group attached to the C2 position of the galactose ring. Additionally, the claimed invention is directed to use of the glycoconjugate in medical therapy.

An adequate written description of the invention may be shown by any description of sufficient, relevant, identifying characteristics so long as a person skilled in the art would recognize that the invention had possession of the claimed invention (M.P.E.P. §2163.04 II.A.3(a)). To satisfy the written description requirement, there is no *in haec verba* requirement, and claims may be supported in the specification through express, implicit, or inherent disclosure (MPEP §2163). Furthermore, a patent specification need not teach, and preferably omits, what is well known in the art." *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384, 231 USPQ 81, 94 (Fed. Cir. 1986).

In particular, the Office Action at page 6 alleges

> In this case, the specification does not reasonably provide a **written description** for (1) the *binding specificity* of the targeting compound such as any glycoprotein, any glycolipid, any carbohydrate or any antibody in the claimed glycoconjugate and (2) the structure associated with function of any bioactive agent, any bioactive agent such as any polypeptide, any releasing factor, any releasing factor inhibitor, any nucleic acid, any vaccine, any xanthine derivative, any genetic material, any herbal remedy joined to any targeting compound by a modified UDP galactose acetyl group, and wherein the modified UDP-Ga1NAc comprises a reactive functional group attached to the C2 position of the galactose ring for use in any medical therapy that encompassed prevention of all diseases.

Applicants respectfully disagree. As set forth above, the measurement of binding specificity and structural features of glycoconjugates are described and, if any experimentation would be required, such experimentation would be routine to one skilled in the art. Targeting compounds are described in the specification at page 10 and page 18. Applicants provide a particular example of antibodies as a targeting compound at p. 20 of the specification. Further, targeting compounds were well known in the art as described above.

Moreover, binding specificity of glycoprotein, glycolipid or carbohydrate targeting compounds was known in the art at the time of filing. For example, antibodies were known in the art at the time of filing to be targeting compounds. In particular, monoclonal antibodies against tumor antigens were known in the art as cancer therapeutic agents at the time of filing. For example, clinical trials were conducted with various monoclonal antibody therapeutics, such

as bevacizumab, a recombinant humanized anti-VEGF monoclonal antibody that has been evaluated in Phase II and Phase II trials, and Ramaswamy et al. (Clin Breast Cancer. 2003 Oct;4(4):292-4, provided herein) describe in combination with doclataxel in women with advanced breast cancer. Vande Putte et al. (Ann Rheum Dis. 2003 Dec;62(12):1168-77, provided herein), evaluate the efficacy and safety of the fully human anti-tumour necrosis factor alpha monoclonal antibody adalimumab (D2E7) in DMARD refractory patients with rheumatoid arthritis: a 12 week, phase II study. Carbohydrate based targeted therapeutics were also well known in the art. For example, insulin is a well known therapeutic. Poulsen et al. (Diabetes Care. 2003 Dec;26(12):3273-9, provided herein), test a combination therapy with insulin as part, rosiglitazone, and metformin to treat reduced insulin secretion and insulin resistance in skeletal muscle and liver in type 2 diabetes. Further, the anticancer compound doxorubicin was well known by one of skill in the art at the time of filing as a targeted anticancer compound. Numerous publications from the time of filing teach the use of doxorubicin in clinical trials (see, e.g. Anton et al., Clin Breast Cancer. 2003 Oct;4(4):286-91, provided herein).

Bioactive agents are described at pages 10 - 18. Further, bioactive agents were well known in the art. Further, it was known in the art at the time of filing that bioactive agents, such as those claimed, could be used to treat various diseases. For example, the Campbell et al. reference (Cancer Res September 1, 2006 66; 8707), provided herein, demonstrates that statins prevent breast cancer growth in vivo and in vitro. The Cascone et al. reference (Ann Oncol. 2006 Mar;17 Suppl 2:ii46-48), provided herein, summarizes the clinical evidence on the anticancer activity of small molecule EGFR inhibitors in small cell lung cancer. Restivo et al. (Diabetes Care. 2006 Dec;29(12):2650-3), provided herein, teach botulinum toxin treatment for oropharyngeal dysphagia associated with diabetic neuropathy. Brennan et al. (N Engl J Med. 2006 Nov 9;355(19):1967-77), abstract provided herein, compare a rabbit antithymocyte polyclonal antibody or basiliximab, an interleukin-2 receptor monoclonal antibody, in renal transplantation graft rejection. Villa et al. (Br J Cancer. 2006 Dec 4;95(11):1459-66. Epub 2006 Nov 21), provided herein, show that a prophylactic quadrivalent HPV vaccine was effective through 5 years for prevention of persistent infection and disease caused by HPV 6/11/16/18.

Applicants have demonstrated that antibodies can be galactosylated with Y289L GalT having a chemical handle at the C2 position in Bioconjugate Chem. 2009, 20, 1228 – 1236 (provided herein). Applicants describe the utility of Y289L GalT to transfer a sugar residue with

C2-keto-Gal (or GalNAz) from their UDP derivatives to the N-acetylglucosamine residue of glycoproteins or glycopeptides. (see, e.g. Figure 5 on page 1233). Moreover, Applicants teach that the conjugation technology is a viable method that can be used for detection and targeting therapies. (see, p.1229). In Bioconjugate Chem. 1009, 20, 1383- 1389 (provided herein), Applicants describe the biological activity of the described glycoconjugates. For example, Applicants describe C-terminal extended fusion polypeptides of recombinant scFv fusion proteins that are used as the acceptor substrate for human polypeptide-alpha-N-acetylgalactosaminyltransferase II that transfers either GalNAc or 2-keto-Gal from their respective UDP-sugars to the side-chain hydroxyl group of the Thr residue(s). The fusion scFv proteins with the modified galactose are then conjugated with a fluorescence probe, Alexa488, that carries an orthogonal reactive group. The fluorescence labeled scFv proteins bind specifically to a human breast cancer cell line (SK-BR-3) that overexpresses the HER2 receptor, indicating that the in vitro folded scFv fusion proteins are biologically active and the presence of conjugated multiple Alexa488 probes in their C-terminal end does not interfere with their binding to the antigen.

The Office at page 20 states:

> Note, amending the claims to recite a glycoconjugate comprising a specific bioactive agent as listed at pages 14-15 and a specific targeting compound such as the ones listed at page 19 wherein the bioactive agent and the targeting compound are joined by a modified UDP galactose-Acetyl group (UDP-Gal1NAc) having a ketone functional group appended at the C-2 position of the galactose ring using the mutant Y289L galactose transferase would obviate this rejection. **One of ordinary skill in the art would be able to envision the structure associated with function of the encompassed claimed glycoconjugate for delivery or targeting the specific biological agent to cancer cell.** (emphasis added).

Applicants respectfully submit that if the subject matter indicated above is adequately described, then one skilled in the art would inherently recognize that Applicants were in possession of therapeutic uses of the claimed invention.

Thus, the originally filed specification shows applicants were in possession of the claimed invention. Clearly, the art supports the various known targeting compounds and bioactive agents, as claimed and taught in the specification, as well as their use. Any person skilled in the art would recognize Applicants were in possession of the claimed invention. Accordingly,

Applicants respectfully request reconsideration and withdrawal of this rejection for lack of written description under 35 U.S.C. §112, first paragraph.

CONCLUSION

In view of the foregoing amendments and arguments, Applicants respectfully request reconsideration and withdrawal of all pending objections/rejections and allowance of the application with claims 1, 2, 43-45, and 49 presented herein. If a telephone call with Applicants' representative would be helpful in expediting prosecution of the application, Applicants invite the Examiner to contact the undersigned at the telephone number shown below.

Dated: February 11, 2011

Respectfully submitted,

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